

10/018222  
2400 Pennsylvania Avenue, NW  
Washington, DC 20037-3213  
202.293.706C  
F 202.293.786C

www.sughrue.com

**Louis Gubinsky, Esq.**  
T (202) 663-7921  
lgubinsky@sughrue.com

December 18, 2001

## BOX PCT

Commissioner for Patents  
Washington, D.C. 20231

PCT/JP00/04440  
-filed July 3, 2000

Re: Application of KAKUYAMA, TSUTOMU  
MEANS FOR STABILIZING HEMOGLOBIN  
**Assignee: INTERNATIONAL REAGENTS CORPORATION**  
Our Ref: Q67737

Dear Sir:

The following documents and fees are submitted herewith in connection with the above application for the purpose of entering the National stage under 35 U.S.C. § 371 and in accordance with Chapter II of the Patent Cooperation Treaty:

- ☑ an executed Declaration and Power of Attorney.
- ☑ an English translation of the International Application.
- ☑ an English translation of Article 34 amendments (annexes to the IPER).
- ☑ an executed Assignment and PTO 1595 form.
- ☑ a Preliminary Amendment
- ☑ an English translation of the IPER

It is assumed that copies of the International Application, the International Search Report, the International Preliminary Examination Report, and any Articles 19 and 34 amendments as required by § 371(c) will be supplied directly by the International Bureau, but if further copies are needed, the undersigned can easily provide them upon request.

The Government filing fee is calculated as follows:

Total claims	<u>12</u>	-	20	=	<u>          </u>	x	\$18.00	=	<u>          </u>	\$0.00
Independent claims	<u>1</u>	-	3	=	<u>          </u>	x	\$84.00	=	<u>          </u>	\$0.00
Base Fee									<u>          </u>	\$890.00
Multiple Dependent Claim Fee									<u>          </u>	\$0.00
<b>TOTAL FILING FEE</b>									<u>          </u>	\$890.00
<b>Recordation of Assignment</b>									<u>          </u>	\$ 40.00
<b>TOTAL FEE</b>									<u>          </u>	\$930.00



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JG07 Rec'd PCT/PTO 18 DEC 2001

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Checks for the statutory filing fee of \$890.00 and Assignment recordation fee of \$40.00 are attached. You are also directed and authorized to charge or credit any difference or overpayment to Deposit Account No. 19-4880. The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16, 1.17 and 1.492 which may be required during the entire pendency of the application to Deposit Account No. 19-4880. A duplicate copy of this transmittal letter is attached.

Priority is claimed from:

Country

JAPAN

Application No

11-188132

Filing Date

July 1, 1999

Respectfully submitted,

Louis Gubinsky

Registration No. 24,835

SUGHRUE MION, PLLC  
2100 Pennsylvania Avenue, N.W.  
Washington, D.C. 20037-3213  
Telephone: (202) 293-7060  
Facsimile: (202) 293-7860

Date: December 18, 2001

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

KAKUYAMA, TSUTOMU

Appln. No.: Not Yet Assigned

Confirmation No.: Unknown

Group Art Unit: Not Yet Assigned

Filed: Herewith

Examiner: Unknown

For: MEANS FOR STABILIZING HEMOGLOBIN

**PRELIMINARY AMENDMENT**

Commissioner for Patents  
Washington, D.C. 20231

Sir:

Prior to examination, please amend the above-identified application as follows:

**IN THE CLAIMS:**

**Please enter the following amended claims:**

3. (Amended) The stabilizing agent for hemoglobin according to claim 1, wherein said sulfur containing material is compound with SH group.
- 6 (Amended) The stabilizing agent for hemoglobin according to claim 1, wherein said sulfur containing compound is added in an amount of 0.01 to 0.0001 parts by weight per 1 part by weight of hemoglobin.
7. (Amended) The stabilizing agent for hemoglobin according of claim 1, wherein said hemoglobin are hemoglobin.
8. (Amended) The stabilizing agent for hemoglobin according to claim 1, wherein said hemoglobin are glycated hemoglobin.

## PRELIMINARY AMENDMENT

9. (Amended) The method for stabilizing hemoglobin, wherein characterized by adding the stabilizing agent for hemoglobin according to claim 1.

10. (Amended) A composition containing hemoglobin, characterized by incorporating the stabilizing agent according to claim 1.

11. (Amended) A kit which comprises at least one of the stabilizing agent according to claim 1 and hemoglobin.

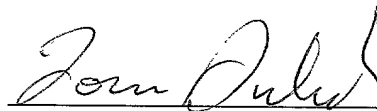
12. (Amended) Use of sulfur containing compound in stabilizing agent for hemoglobin according to claim 1.

PRELIMINARY AMENDMENT

REMARKS

The claims assuming entry of the Rule 34 Amendments are amended to delete multiple claim dependency. Entry and consideration of this Amendment is respectfully requested.

Respectfully submitted,



Louis Gubinsky  
Registration No. 24,835

SUGHRUE MION, PLLC  
2100 Pennsylvania Avenue, N.W.  
Washington, D.C. 20037-3213  
Telephone: (202) 293-7060  
Facsimile: (202) 293-7860

Date: December 18, 2001

PRELIMINARY AMENDMENT

APPENDIX

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

The claims are amended as follows:

3. (Amended) The stabilizing agent for hemoglobin according to claim 1 ~~or 2~~, wherein said sulfur containing material is compound with SH group.
- 6 (Amended) The stabilizing agent for hemoglobin according to ~~any of claim 1 to 5~~, wherein said sulfur containing compound is added in an amount of 0.01 to 0.0001 parts by weight per 1 part by weight of hemoglobin.
7. (Amended) The stabilizing agent for hemoglobin according to ~~any of claim 1 to 6~~, wherein said hemoglobin are hemoglobin.
8. (Amended) The stabilizing agent for hemoglobin according to ~~any of claim 1 to 6~~, wherein said hemoglobin are glycated hemoglobin.
9. (Amended) The method for stabilizing hemoglobin, wherein characterized by adding the stabilizing agent for hemoglobin according to ~~any of claim 1 to 8~~.
10. (Amended) A composition containing hemoglobin, characterized by incorporating the stabilizing agent according to ~~any of claim 1 to 8~~.
11. (Amended) A kit which comprises at least one of the stabilizing agent according to ~~any of claims 1 to 8~~ claim 1 and hemoglobin.
12. (Amended) Use of sulfur containing compound in stabilizing agent for hemoglobin according to ~~any of claims 1 to 8~~ claim 1.

## Specification

### Title of the Invention

Means for stabilizing hemoglobin

### Field of the Invention

The present invention relates to a method for stabilizing hemoglobin and a composition containing the same.

### Background of the Invention

Hemoglobin is a hem-protein existed in red blood cell, which is constituted with tetramer consisting of 2 pair of polypeptide chains, (each chain is bound to 1 mol hem), named as  $\alpha$ - and  $\beta$ -chains, and having 65,000 of molecular weight. The hemoglobin are contained in blood in an amount of 16 to 18 g/dL for male, and 14 to 16 g/dL for female, and play an oxygen transporting function by reversively detaching oxygen to iron molecule.

Because of maintaining such a rule, a measurement of the hemoglobin is one of the basic measurement items in a clinical laboratory test, and is utilized as a diagnosis of anemia, i.e., iron deficiency anemia, hypoplastic anemia, hemolytic anemia, and etc., in combination with red corpuscle number and hematocric value. Recently, by detecting an extremely small amount of hemoglobin contained in a stool, the measurement takes advantage in determination for a diagnosis of colon cancer.

On the other hand, a glycated hemoglobin is produced by non-enzyme reaction between hemoglobin and glucose. A measurement of the glycated hemoglobin in blood is reflected with a control of blood sugar concentration for past 3 or 4 weeks, and is effectively available as an indication of blood sugar concentration in long term, which

is not affected by daily meals. In the present specification, hereinafter, a term of hemoglobin is used, as totally including hemoglobin and glycated hemoglobin.

At present, the measurement of the hemoglobin in clinical laboratory takes place with HPLC method, immunological method, affinity method, electrophoresis method, isoelectric fraction method, TBA (2-thiobarbituric acid) method, RIA (Radio Immuno Assay) method, Photic acid method, furosine determination method, and the like.

On measuring the hemoglobin above, a substance which may be of standard and control material, is required. However, the hemoglobins are unstable, and lose oxygen binding function, and a hem iron is changed from  $\text{Fe}^{2+}$  to  $\text{Fe}^{3+}$ , by oxidation and are changed in color from clear red to dark brown. Furthermore, the hemoglobin are noted to be oxidized to methemoglobin, even by exposing thereof to air, and by lyophilization.

As a method for protecting such an oxidization, there is a method for which, on a site, where an oxygen is to be bound, two moles atoms, such as CO, NO, CN, etc., which have almost the same diameter as of oxygen, are previously bound, or a method for adding sodium azide on lyophilization step. However, these methods have drawbacks that operations are in troublesome; one of the methods provides significantly inadequate low amount, or another is impossible operability. Besides these, a disposal trouble on sodium azide arose due to poisoness. Further, even though a method for adding a compound containing nitrogen is disclosed in the publication (Laid-open Japanese Patent Publication No. Sho 60-35270), an effect for preventing separation of free iron form from hemoglobin is merely disclosed. A method for incorporating glucose and amino acids (Laid-open Japanese Patent Publication No. Sho 61-1620) discloses a protecting agent for oxidizing hemoglobin to methemoglobin, an object of the method, however, is to stabilize hemoglobin which are used as a substitute blood having a concentration mg/mL level, as hemoglobin. Thus, these methods are not acceptable for stabilizing hemoglobin having a concentration in



ng to  $\mu\text{g/mL}$ , which is required in clinical laboratory test as a standard or control material. Another method for stabilizing hemoglobin by incorporating amino acid and albumin is published (Laid-open Japanese Patent Publication No. Hei 8-245421), however, the method is restricted in a composition of the agent, because this method is required to use albumin other than amino acid.

As discussed above, conventional method for stabilizing the hemoglobin is not suitable as a method for stabilizing control material and standard material, which are required for accurate measuring hemoglobin in a clinical laboratory test. Accordingly, the method for stabilizing control material and standard material containing hemoglobin, are highly desired in the field of pharmaceutical and clinical laboratory test.

### **Description of the Invention**

As the result of a study on a stabilization of the control material and the standard material, the present inventors were found that the stability of hemoglobin were improved by incorporating with sulfur containing material, particularly compound with SH group, thereby establishing the present invention.

That is, one of the gists of the present invention is to provide a stabilizing agent for hemoglobin, characterized by stabilizing hemoglobin in a state of solution.

The sulfur containing agent of the present invention is of compound with SH group.

Besides these, according to the present invention, said compound with SH group may be one of the compound selected from the group consisting of, sulfur containing amino acid, such as cysteine, methionine, cystine, and etc., and family thereof; and sulfur containing compound, such as thioglycol acid, 1-thioglycelin, thiodiglycol, mercaptoethanol, glutathione, dithiothreitol and etc., and family thereof.

According to the present invention, compound with SH group may be cysteine and family thereof.

The present invention is characterized in that the sulfur containing compound is contained in an amount of 0.01 to 0.00001 part by weight based on 1 weight part of hemoglobin.

According to the present invention, said hemoglobin may be hemoglobin.

According to the present invention, said hemoglobin may be glycated hemoglobin.

Another gist of the present invention is a method for stabilizing of the present invention.

Further gist of the invention is a composition characterized by incorporating with the stabilizing agent for hemoglobin of the present invention.

Still further gist of the present invention is at least incorporating the stabilizing agent for hemoglobin and hemoglobin of the present invention.

Still another gist of the invention is use of the sulfur containing compound in the stabilizing agent of the present invention.

#### **Best mode for carrying out the Present Invention**

According to the present invention, the hemoglobin mean hemoglobin and glycated hemoglobin. An example of the glycated hemoglobin includes HbA<sub>1c</sub>. And another example of the hemoglobin includes HbA<sub>1a</sub>, HbA<sub>1b</sub>, HbF, HbA<sub>0</sub>, HbA<sub>2</sub>, oxyhemoglobin, carbonylhemoglobin, methohemoglobin, cyanomethohemoglobin, alkali modified hemoglobin, and the like, and other heterohemoglobin. Besides these, modified hemoglobin, such as phosphate ester derivatives of hemoglobin, hemoglobin-polyalkylene conjugates, hemoglobin-inuren conjugates, and hemoglobin-haptoglobin complexes, are also included in the present invention. Further, the hemoglobin of the present invention may be available not only in human origin,

but also animal origin, for example, cow, pig, sheep, horse, dog, monkey, rabbit, chicken, and the like. These are used as a standard or control material for various in a dried substance, as a lyophilized agent, and maybe in a form of dried agent, liquid agent, etc., if desired.

The first and principal gist of a stabilizing method and stabilizing agent for hemoglobin according to the present invention, resides in insuring a stability of the hemoglobin in a liquid state. It is meant by securing stability of the hemoglobin in dried remedy and in a state of solution.

A stabilizing method for the hemoglobin according to the present invention is to incorporate sulfur containing compound in order to stabilize thereof. Addition of the sulfur containing compound is more convenient by adding in a process for preparing agent, however, may be attained by conventionally adding after dissolving the agent, on demand. The hemoglobin standard material and control material, in which the hemoglobin is the main ingredient and the sulfur containing compound is contained as a stabilizing agent, are provided, by adding the sulfur containing agent in a step for preparing agent. If the agent is to be the type, of which the compound is added on demand, the main ingredient and the stabilizing agent containing sulfur containing agent are separately prepared in a form of a kit product.

As the sulfur containing agent according to the present invention, compound with SH group is well-known and widely available. Compound with SH group includes sulfur containing amino acid, such as cysteine, methionine, etc.; sulfur containing compound, such as thiobenzoic acid, thioglycol acid, 1-thioglycerine, thiodiglycol, mercaptoethanol glutathione, dithiothreitol, etc., and family thereof. These may be used singly or in combination. The most preferable is the sulfur containing amino acid, such as cysteine, methionine, cystine, and the like, and family thereof. The particularly preferably is cysteine and family thereof.

Amount of the sulfur containing agent to be used is 0.01 to 0.00001

part by weight per 1 part by weight of the hemoglobin, preferably 0.001 to 0.0001 part by weight. A concentration of a solution, when the agent is prepared in a form of solution, is 0.01 to 100 mM, preferably 0.1 to 10 mM, per hemoglobin of 2 to 10 weight % concentration.

The standard material or control material containing hemoglobin, which is provided and assures stability according to the present invention, may be said as a composition containing hemoglobin. Said composition may be incorporated under applying a well-known techniques, in addition of the main ingredient and stabilizer, as base component, with bulking agents, pH control agents for protecting turbidity on solubility thereof, protein, sucrose, high molecular weight compounds, inorganic salts, chelating agents, and the like, or may be combined thereof, on demand.

Example thereof includes various buffer solution or pH control agent, which is capable of controlling pH of 5 to 9, protein such as albumin, gelatin, etc., saccharide, such as glycerol, sucrose, (preferably disaccharide such as sucrose), etc., polysaccharide, such as sodium sulfate dextran, heparin, sodium sulfate, chondroitin, dextran, etc., and high molecular compound such as polyethyleneglycol, polyvinylalcohol, polyvinyl pyrrolidone, polypropylene glycol, etc. These materials may be used singly, or in combination. Besides these, saccharides such as glucose, maltose, inositol, fructose, glucitol, glucono- $\delta$ -lactone, trehalose, maltitol, raffinose, mannitol; inorganic compound such as sodium chloride, sodium phosphate, potassium chloride, calcium lactate, etc., chelating agent such as EDTA (ethylenediaminetetraacetic acid), NTA (nitrilotriacetic acid), EDDA (ethylenediaminediacetic acid), CyDTA (trans-1,2-Diaminocycloheane-N,N,N',N'-tetraacetic acid monohydrate), DPTA-OH (1,3-Diamino-2-hydroxypropane N,N,N',N'-tetraacetic acid), DTPA (Diethylenetriamine-N,N,N',N'',N''-pentaacetic acid), EDDP (Ethylenediamine-N,N'-dipropionic acid, dihydrochloride), EDDPO [Ethylenediamine-N, N'-bis(methylenephosphonic acid),

hemihydrate], EGTA [Ethyleneglycol-bis-( $\beta$ -amino-ethylether) tetraacetic acid], HBED [N,N'-bis(2-hydroxybenzyl) ethylenediamine-N,N-diacetic acid], HDTA (1,6-Hexamethylenediamine-N,N,N',N'-tetraacetic acid), HIDA [N-(2-Hydroxyethyl) iminodiacetic acid], IDA (Iminodiacetic acid), NTP (Nitrilotripropionic acid), NTPO [Nitrilotris (methylenephosphonic acid), trisodium salt], TTHA (Triethylenetetramine-N,N,N',N'',N''',N'''-hexaacetic acid), etc.,  $\alpha$ -,  $\beta$ -,  $\gamma$ -CD (cyclodextrin), or these CD modified with polymer, and the like. These may be used singly or in combination.

### Examples

The present invention is explained in more detailed with referring to the following examples, which are not extruded as restricting the present invention.

#### (Example 1)

The mixture of, an agents stated below, were prepared with or without adding 1 mM L-cysteine, 1 mL mixture were pipetted into 5 mL glass vessel, and were lyophilized to form lyophilized preparation. As hemoglobin, hemoglobin standard containing HbA<sub>1a</sub>, HbA<sub>1b</sub>, HbF, and HbA<sub>0</sub> were used, and added in a concentration of 7%.

10 mM	Phosphate buffer solution (pH 7.0)
25 mM	EDTA·2Na
7 %	Hemoglobin standard (JML company)
25 %	Sucrose

#### (Experimental Example 1)

Each of the lyophilized agents, with or without incorporating L-cysteine, which were prepared in the Example 1, was dissolved in

1 mL distilled water, to compare stability of the hemoglobin in a state of solution, at 25 °C, after 25 hours elapse of time. Measurement of the hemoglobin was performed by detecting absorbance (O. D. value) at 577 nm. (Method in Enzymology, 188, 266-272). From the results, as shown in the Table 1, by adding L-cysteine, a sufficient stabilizing effect of the hemoglobin in a state of solution was confirmed. Further, a chemical analysis of each portion using an automatic glycosylated hemoglobin analyzer HLC-723GHbIII, manufactured by Toso company. These results showed that was stable in all kinds of hemoglobin fractions.

Table 1

	0 Hour	25 Hour
With L-cysteine adding	0.86	0.85
Without L-cysteine	0.86	0.41

(Example 2)

A sample was prepared with the agent, stated below, by adding with or without adding 1 mM L-cysteine. In the same manner, as stated in the Example 1, the hemoglobin standard containing HbA<sub>1c</sub>, HbA<sub>1a</sub>, HbF, and HbA<sub>0</sub> was used in order to make a concentration of hemoglobin in 7%.

10 mM	Phosphate buffer solution (pH 7.0)
25 mM	EDTA 2 Na
7 %	Hemoglobin standard (JML company)

(Experimental Example 2)

Each of the agents, with or without incorporating L-cysteine, which were prepared in the Example 2, was studied in comparing stability of hemoglobin after preparation, and at 25 °C after 25 hours elapse of time, in the same manner as of the Experimental Example 1. The results were shown in Table 2. According to adding cysteine, a

sufficient stability of the hemoglobin was obtained, regardless of presence of sucrose. Further, chemical analysis of each portion was carried out using Automatic Analyzer of glycohemoglobin HLC-723GHbIII. These results showed that was stable in all kinds of hemoglobin fractions.

Table 2

	0 Hour	25 Hour
With L-cysteine adding	0.85	0.85
Without L-cysteine	0.85	0.43

#### Possibility in commercially available

By the stabilizing method for hemoglobin and stabilizing agent, characterized in adding sulfur containing compound according to the present invention, the stability of hemoglobin and glycated hemoglobin in a state of solution was secured. Thus, by introducing stabilizing means for hemoglobin, for example, a stability of a standard material and controlling material containing hemoglobin for clinical laboratory test, was improved and was resulted in expecting high accurate laboratory test results. The present invention is useful for contributing in clinical laboratory test and pharmaceutical field.

What is claimed is;

1. A stabilizing agent for hemoglobin characterized in incorporating sulfur containing compound
2. The stabilizing agent for hemoglobin according to claim 1, wherein characterized by stabilizing hemoglobin in a state of solution.
3. The stabilizing agent for hemoglobin according to claim 1 or 2, wherein said sulfur containing material is compound with SH group.
4. The stabilizing agent for hemoglobin according to claim 3, wherein said compound with SH group is one or more compound selected from cysteine, methionine, or sulfur containing amino acid, such as cystine or family thereof, sulfur containing compound such as thio benzoic acid, thio glycol acid, 1-thio glycerin, thiodiglycol, mercaptoethanol, gulutathione, orthioglycerol, or family thereof.
5. The stabilizing agent for hemoglobin according to claim 3, wherein said compound with SH group is cysteine or family thereof.
6. The stabilizing agent for hemoglobin according to any of claims 1 to 5, wherein said sulfur containing compound is added in an amount of 0.01 to 0.0001 parts by weight per 1 part by weight of hemoglobin.
7. The stabilizing agent for hemoglobin according to any of claims 1 to 6, wherein said hemoglobin are hemoglobin.
8. The stabilizing agent for hemoglobin according to any of claims 1 to 6, wherein said hemoglobin are glycated hemoglobin.
9. The method for stabilizing hemoglobin, wherein characterized by adding the stabilizing agent for hemoglobin according to any of claims 1 to 8.
10. A composition containing hemoglobin, characterized by incorporating the stabilizing agent according to any of claim 1 to 8.
11. A kit which comprises at least one of the stabilizing agent according to any of claims 1 to 8 and hemoglobin.
12. Use of sulfur containing compound in stabilizing agent for hemoglobin according to any of claims 1 to 8.



**DECLARATION AND POWER OF ATTORNEY FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63)**

As a below named inventor, I hereby declare that: My residence, mailing address, and citizenship are as stated below next to my name. I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

**MEANS FOR STABILIZING HEMOGLOBIN**

the application of which

☒ is attached hereto

OR

☐ was filed on \_\_\_\_\_ as United States Application Number or PCT International Application Number \_\_\_\_\_ (Confirmation No. \_\_\_\_\_), and was amended on \_\_\_\_\_ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified application, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56, including for continuation-in-part application(s), material information which became available between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part application.

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or (f), or 365(b) of any foreign application(s) for patent, inventor's or plant breeder's rights certificate(s), or 365(a) of any PCT international application(s) which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application(s) for patent, inventor's or plant breeder's rights certificate(s), or any PCT international application(s) having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date	Priority Claimed	
			Yes	No
Hei11-188132	Japan	July 01, 1999	<input checked="" type="checkbox"/>	<input type="checkbox"/>

I hereby claim domestic priority benefits under 35 United States Code §120 of any United States application(s), §119(e) of any United States provisional application(s), or §365(c) of any PCT International application(s) designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in a listed prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge my duty to disclose any information material to the patentability of this application as defined in 37 C.F.R. 1.56 which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

Prior U.S. or International Application Number(s)	U.S. or International Filing Date	Status
PCT/JP00/04440	03/07/00	

I hereby appoint all attorneys of **SUGHRUE MION, PLLC** who are listed under the USPTO Customer Number shown below as my attorneys to prosecute this application and to transact all business in the United States Patent and Trademark Office connected therewith, recognizing that the specific attorneys listed under that Customer Number may be changed from time to time at the sole discretion of Sughrue Mion, PLLC, and request that all correspondence about the application be addressed to the address filed under the same USPTO Customer Number.



23373

PATENT TRADEMARK OFFICE

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

**NAME OF SOLE OR FIRST INVENTOR:**

Given Name (first and middle [if any]) <u>100 KAKUYAMA Tsutomu</u>		Family Name or Surname	
Inventor's Signature <u>Tsutomu Kakuyama</u>		Date <u>9/Dec./2001</u>	
Residence: City <u>Kobe</u>	State <u>Hyogo</u>	Country <u>JPN</u>	Citizenship <u>Japanese</u>
c/o Research & Development Center, International Reagents Corporation, 1-2 Mailing Address: Murotani 1-chome, Nishi-ku, Kobe-shi, Hyogo 651-2241 Japan			
City <u>Kobe</u>	State <u>Hyogo</u>	Zip <u>651-2241</u>	Country <u>Japan</u>

**NAME OF SECOND INVENTOR:**

Given Name (first and middle [if any])		Family Name or Surname	
Inventor's Signature		Date	
Residence: City	State	Country	Citizenship
Mailing Address:			
City	State	Zip	Country

**NAME OF THIRD INVENTOR:**

Given Name (first and middle [if any])		Family Name or Surname	
Inventor's Signature		Date	
Residence: City	State	Country	Citizenship
Mailing Address:			
City	State	Zip	Country

**NAME OF FOURTH INVENTOR:**

Given Name (first and middle [if any])		Family Name or Surname	
Inventor's Signature		Date	
Residence: City	State	Country	Citizenship
Mailing Address:			
City	State	Zip	Country

**NAME OF FIFTH INVENTOR:**

Given Name (first and middle [if any])		Family Name or Surname	
Inventor's Signature		Date	
Residence: City	State	Country	Citizenship
Mailing Address:			
City	State	Zip	Country